International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 6 Issue 7, November-December 2022 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

A Model of Insulin-Glucose Concentration for Oral Ingestion of 75g of Glucose for Type-I Diabetes Management

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ABSTRACT

The regulation of glucose concentration in the body has triggered more often the stimulant approach. The hourly operation of insulin-glucose-dependent bodily functions has left many type-I diabetic patients with a lot of pain. Doctors have proposed various measures such as oral ingestion of glucose to trigger insulin production to increase glucose uptake in the body. Such measures have not been mathematically modeled. In the current, a mathematical model formulating the concentration of glucose and insulin where extra glucose intake leads to extra stimulation of insulin production has been presented. The mathematical rigor such as the well-posedness of the system indicated that the proposed model is applicable in real-life applications. Numerical simulation indicates that both glucose and insulin concentration continuously increases, a sign of a need to find an optimal control strategy in order to manage type-I diabetes. A sensitivity analysis showed a constant rate of insulin-independent glucose disappearance is the most sensitive in the model. Optimal control investigation indicated that increasing the constant rate of insulin-independent glucose disappearance is effective after 15th hour. Future studies need to consider including other parameters, such as glucose accelerated loss due to exercise in the system.

KEYWORDS: *Oral 75g glucose intake, Glucose concentration, Insulin Concentration, Insulin Stimulant*

How to cite this paper: Irene Melly Chebet | Rotich Titus | Bitok Jacob "A Model of Insulin-Glucose Concentration for Oral Ingestion of 75g of Glucose for Type-I Diabetes Management" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-6 | Issue-7, December 2022, pp.363-369, URL: www.ijtsrd.com/papers/ijtsrd52338.pdf

IJTSRD52338

1. INTRODUCTION

Regular human insulin production in the body begins to function after 30-60 min, and the peak concentration is witnessed after 2-4 hours [1]. The adverse effects are felt between 5 to 22 hours. However, there is no clarity on whether extra glucose usually taken by the patients effectively manages these effects.

Usually, 75g of glucose is taken orally to stimulate insulin production to regulate glucose concentration [2]. Absurdity often occurs when the patients take extra glucose but still experience the side effect of excess glucose in the body, which often leads to type-I diabetes.

Mathematically, the oral ingestion of glucose to stimulate insulin production for glucose uptake by the body has not been studied. The biological interpretation of these phenomena has not been widely received with open understanding. Biologically, inter-organ dependence has dominated the research area [3, 4], leaving a hole in the mathematical perspective.

Contribution

The proposed study has two major contributions

1. The glucose intake to stimulate insulin production is evaluated to ascertain its effects on the overall glucose concentration in the body.
2. Establishing an optimal control of the system to regulate the glucose concentration in the body in the presence of extra glucose and insulin production.

The rest of the paper is organized as follows: Section 2 presents the model formulated and governing equations. Section 3 the wellposedness of the system, investigating the system application in real life. Section 4 presents the equilibrium of the system, such as disease-free equilibrium and endemic equilibrium, and basic reproductive number. Section 5 presents the

estimation of parameter values, sensitivity analysis, and numerical simulation of glucose concentration and insulin in the body. Section 6 presents a formulation of the optimal control of the system. Section 7 presents the conclusion of the study.

2. Proposed Study

2.1. The model formulation

The model presented in Figure 1 shows the interaction between glucose G and insulin I concentration in the body. Glucose is increased in the body at a constant rate Π_2 due to body metabolism such as food conversion. It is also increased in the body at a constant rate Ψ_2 due to $75g$ of glucose intake. It is depleted at a constant rate σ_2. Insulin concentration in the body is increased due to oral ingestion of glucose of $75g$ at rates Φ_2. The insulin is decrease at rate and η_2 due to a constant rate insulin degradation and a constant rate insulin-dependent glucose disappearance η_2.

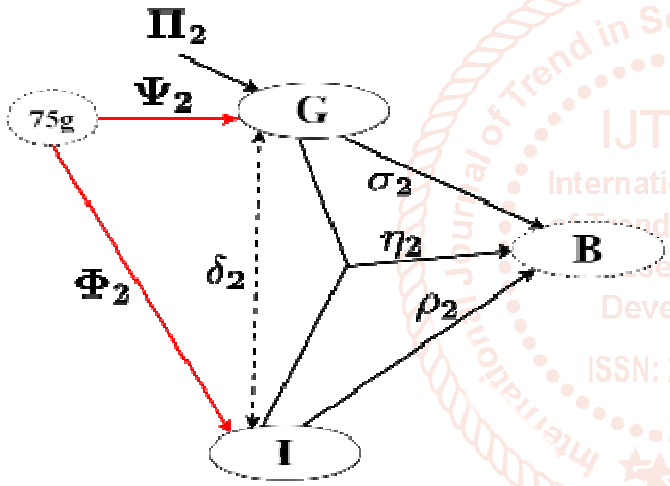


Figure 1: A model formulating the interaction between glucose and insulin.

2.2. The governing equations

$$\frac{dG}{dt} = \Pi_2 + \Psi_2 - (\sigma_2 + \eta_2 I)G \quad (1)$$

$$\frac{dI}{dt} = \Phi_2 - \rho_2 I - \eta_2 IG \quad (2)$$

with $G > 0, I > 0$.

3. Well-posedness

3.1. Existence of the solution

We show that the model (1) - (2) solution is unique, non-negative, and bounded, making it applicable in real life. Let $X(t) = (G(t), I(t))$ and $f: X = G'$ such that $f = (f_1, f_2)$, where

$$f_1(X) = \Pi_2 + \Psi_2 - (\sigma_2 + \eta_2 I)G \quad (3)$$

$$f_2(X) = \Phi_2 - \rho_2 I - \eta_2 IG \quad (4)\ (5)$$

So that equations (1) - (2) can be written as

$$X' = f(X(t)); X(0) = (G_0, I_0) \quad (6)$$

Theorem 3.1 *Suppose $f(X(t))$ is given by (6), with its initial condition $X(0) = G + I > 0$, is non-negative. System (1)-(2) solution is unique, non-negative, and bounded.*

Proof. if f_i are continuous functions and $\frac{\partial f_i}{\partial x_j}$: $1 \le i, j \le 2$ exists then $f(X(t))$ is locally Lipschitz continuous. $X(0) = G + I > 0$. Therefore, at least one compartment is non-empty. This means that a unique solution $X(t)$ of the system exists, defined in some time interval containing $t = 0$ [5]. If we let t_0 be the smallest t such that $G(t_0) = 0$ or $I(t_0) = 0$. We use continuity of $G(t)$, and $I(t)$, $\exists\ t^* > t_0$ such that if $G(t_0) = 0$, then from (1) to show that $\frac{dG}{dt} = \Pi_2 + \Psi_2 > 0$, $\forall t \in [t_0, t^*]$. This means that G is an increasing function on interval $[t_0, t^*]$, which in turn means that $G(t) \ge 0 \forall t \in [t_0, t^*]$. We use the same approach to show that, if $I(t_0) = 0$, then from (1) we get that $\frac{dI}{dt} = \Phi_2 \ge 0 \longrightarrow I(t) > 0 \forall t \in [t_0, t^*]$. Thus, the solution to the system is non-negative. We use the dissipativity condition of theorem 2.3.6 in [6] to show that the solution of the system (1)-(2) exist globally as follows;

$$\begin{aligned} f(X).X &= (f_1, f_2)) \\ &= Gf_1 + If_2 \\ &\le G(\Pi_2 + \Psi_2 - G(\sigma_2 + I\eta_2)) + \\ &\quad I(\Phi_2 - I(\rho_2 + G\eta_2)) \end{aligned} \quad (7)$$

Therefore, a unique solution $X(t) \exists \forall t \ge 0$. Hence the solution is bounded.

4. Stability Analysis

4.1. Endemic Equilibrium

The equilibrium state is defined as when there is no change in the system, $\frac{d}{dt} = 0$. Endemic equilibrium is when $\frac{d}{dt} = 0$, but no state variable is zero, that is, $I \neq 0$ and $G \neq 0$. We derive the endemic equilibrium as follows;

We use (1) to get;

$$G^* = \frac{\Pi_2 + \Psi_2}{\sigma_2 + \eta_2 I^*}. \quad (8)$$

We also use (2) to get;

$$G^* = \frac{\Phi_2 + \rho_2 I^*}{\eta_2 I^*} \quad (9)$$

We use (8) and (9) to get.

$$I^* = \frac{-\left(\Pi_2\eta_2 - \Phi_2\eta_2 + \Psi_2\eta_2 + \rho_2\sigma_2 - K_1^{\frac{1}{2}}\right)}{2\eta_2\sigma_2} \quad (10)$$

$$K_1 = (\Phi_2^2\eta_2^2 - 2\Phi_2\Pi_2\eta_2^2 - 2\Phi_2\Psi_2\eta_2^2 + 2\Phi_2\eta_2\rho_2\sigma_2 + \Pi_2^2\eta_2^2 + 2\Pi_2\Psi_2\eta_2^2 + 2\Pi_2\eta_2\rho_2\sigma_2 + \Psi_2^2\eta_2^2 + 2\Psi_2\eta_2\rho_2\sigma_2 + \rho_2^2\sigma_2^2)$$

4.2. Disease Free Equilibrium

The disease-free equilibrium, $\frac{d}{dt} = 0$ but $G_0^* \geq 0$ and $I_0^* \geq 0$.We follow algebraic manipulations to show that $G_0^* = \frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}$, $I_0^* = \Phi_2$. *Hint* we assume the $-\rho_2 I - \eta_2 IG = 0$.

4.3. The Basic Reproduction Number

We follow the works of [5, 6] to compute R_0 as follows:

$$\mathcal{F} = \begin{pmatrix} \eta_2 IG \\ \eta_2 IG \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} \sigma_2 G \\ \rho_2 I \end{pmatrix} \tag{11}$$

We compute the jacobian matrix to attain

$$F = \begin{pmatrix} \eta_2 I & \eta_2 G \\ \eta_2 I & \eta_2 G \end{pmatrix}, \quad V = \begin{pmatrix} \sigma_2 & 0 \\ 0 & \rho_2 \end{pmatrix}. \tag{12}$$

We attain F at the DFE as;

$$F_{DFE} = \begin{pmatrix} \eta_2\Phi_2 & \eta_2\left(\frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}\right) \\ \eta_2\Phi_2 & \eta_2\left(\frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}\right) \end{pmatrix}, \tag{13}$$

We compute the inverse of V as

$$V^{-1} = \begin{pmatrix} \frac{1}{\sigma_2} & 0 \\ 0 & \frac{1}{\rho_2} \end{pmatrix}. \tag{14}$$

We use (13) and (14) to compute FV^{-1} as follows;

$$\begin{pmatrix} \frac{\Phi_2\eta_2}{\sigma_2} & \frac{\eta_2(\Pi_2+\Psi_2)}{\rho_2(\sigma_2+\Phi_2\eta_2)} \\ \frac{\Phi_2\eta_2}{\sigma_2} & \frac{\eta_2(\Pi_2+\Psi_2)}{\rho_2(\sigma_2+\Phi_2\eta_2)} \end{pmatrix} \tag{15}$$

We compute the eigenvalue to get R_0 as;

$$R_0 = \frac{\eta_2}{\rho_2\sigma_2}\left(\rho_2\Phi_2 + \frac{\sigma_2[\Pi_2+\Psi_2]}{\sigma_2+\Phi_2\eta_2}\right) \tag{16}$$

η_2 is the constant rate of decrease of glucose concentration due to insulin-dependent constant rate, ρ_2 is the constant rate of insulin degradation; thus, $\sigma_2\rho_2$ is the rate of degradation of insulin- and glucose in the body. Π_2 is the glucose intake in the body, and σ_2 is the constant glucose disappearance. Ψ_2 is the oral ingestion of glucose, and Φ_2 is insulin increased due to oral ingestion of 75g of glucose. Therefore, R_0 is the sum of the constant rate of glucose and insulin reduction in the body.

4.4. Stability of DFE

4.5. Local stability analysis of the DFE

Theorem 4.1 *Suppose* $X_0 = \left(\frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}, \Phi_2\right)$ *is a DFE for the system (1) and (2), then* X_0 *is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$ *where* R_0 *is defined by* (16).

Proof. See proof of Theorem 4.1 in [7].

4.6. Global stability analysis of the DFE

Theorem 4.2 *Suppose* $R_0 \leq 1$*, the DFE of system (1) and(2) is globally asymptotically stable in* $\Omega = \{X = (G,I) \in \mathbb{R}^2 : G + I \leq C_{GI}$ *and If* $R_0 > 1$*, the DFE is unstable.*

Proof. We use a matrix-theoretic method as suggested by [7]. We assume $x = (G,I)^T$ and $y = (G,I)$. We consider F, V, F and V as defined in Section ??; then

$$\frac{dx}{dt} = F(x,y) - V(x,y),$$

and dynamics of infected compartments is given by

$$\frac{dx}{dt} = (F - V)x - f(x,y),$$

thus, we can obtain $f(x,y)$ as follows

$$f(x,y) = (F-V)x - F(x,y) + V(x,y)$$
$$= \begin{pmatrix} G\sigma_2 - G(\sigma_2 - I\eta_2) - GI\eta_2 & G\sigma_2 + G^2\eta_2 - GI\eta_2 \\ I\rho_2 + I^2\eta_2 - GI\eta_2 & I\rho_2 - I(\rho_2 - G\eta_2) - GI\eta_2 \end{pmatrix}, \tag{17}$$

while

$$V^{-1}F = \begin{pmatrix} \frac{\Phi_2\eta_2}{\sigma_2} & \frac{\eta_2(\Pi_2+\Psi_2)}{\sigma_2(\sigma_2+\Phi_2\eta_2)} \\ \frac{\Phi_2\eta_2}{\rho_2} & \frac{\eta_2(\Pi_2+\Psi_2)}{\rho_2(\sigma_2+\Phi_2\eta_2)} \end{pmatrix}.$$

We see that $F \geq 0$, $V^{-1} \geq 0$, $f(x,y) \geq 0$, $f\left(x, \left(\frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}, \Phi_2\right)\right) = 0$ in Ω. It is also clear that $V^{-1}F$ is reducible. We can therefore construct a Lyapunov function based on Theorem 2.1 and 2.2 as stated by [8]. We denote the left eigenvectors of $V^{-1}F$ corresponding to the eigenvalue of R_0 by $\{v_1, v_2\}$.

Then

$$(v_1, v_1)V^{-1}F = R_0(v_1, v_2)$$

or

$$(v_1, v_2)V^{-1}F = \left(\Phi_2\eta_2\left(\frac{v_2}{\rho_2} + \frac{v_1}{\sigma_2}\right) \quad \frac{\Pi_2+\Psi_2}{\sigma_2+\Phi_2\eta_2}\left(\frac{\eta_2 v_2}{\rho_2} + \frac{\eta_2 v_2}{\sigma_2}\right)\right), \tag{18}$$

and

$$R_0(v_1, v_2) = \frac{\eta_2}{\rho_2\sigma_2}\left(\rho_2\Phi_2 + \frac{\sigma_2[\Pi_2+\Psi_2]}{\sigma_2+\Phi_2\eta_2}\right)(v_1, v_2) \tag{19}$$

We use equations (18) and (19) to derive a possible solution of v_1, v_2. To allow work-ability, let $v_1 = v_2 = 1$. Thus, by Theorem 2.1 of [8], we have $Q = v_t V^{-1} x$ as the Lyapunov function of the model is given by;

$$Q = v_t V^{-1} x$$
$$= \frac{G}{\sigma_2} + \frac{I}{\rho_2}$$

We differentiate Q at DFE to get

$$Q|_{DFE}' = (R_0 - 1)v_t x - v_t V^{-1} f(x,y)$$
$$\neq 0$$

This implies that $x = 0$ and $f(x,y) = 0$ or $y = (G,I)^T = \left(\frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}, \Phi_2\right)^T$. Therefore, $\left(\frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}, \Phi_2\right)$ is the only invariant set in Ω where $Q' = 0$. Thus, by LaSalle's invariance principle [9], the DFE, $\left(\frac{\Pi_2+\Psi_2}{\sigma_2+\eta_2\Phi_2}, \Phi_2\right)$ is globally asymptotically stable in Ω and $R_0 > 1$.

5. Numerical SImulation

5.1. Parameter Estimation

Table 1 gives a description and approximate values of the parameters.

Table 1: Parameters description and values

Parameter	Description	Values $(mg/dL/h)$	Range $(mg/dL/h)$	Source
Φ_2	Insulin increased into the body due 75g glucose intake	275	250-300	[10]
Ψ_2	Glucose increase into the body due 75g glucose intake	75000	-	[10]
Π_2	Glucose infused into the body	1.56	1.4-1.7	[11]
η_2	Constant rate insulin-dependent glucose disappearance	3.8×10^{-8}	$2.8 \times 10^{-8} - 5.\times 10^{-8}$	[11]
ρ_2	Constant rate insulin degradation	0.0437	0.01-0.1	[11]
σ_2	Constant rate insulin-independent glucose disappearance	0.0226	0.01-0.09	[11]

5.2. Sensitivity analysis of the parameters

We perform sensitivity analysis to determine the most influential parameters on R_0 given by (16). This will inform the decision on the parameter that influences the concentration of G and I. Sensitivity analysis is useful in showing the closeness and relatedness of the parameters. A smaller change in parameter may result in a bigger change in R_0. Figure 2 summarizes sensitivity analysis for the model parameters to R_0.

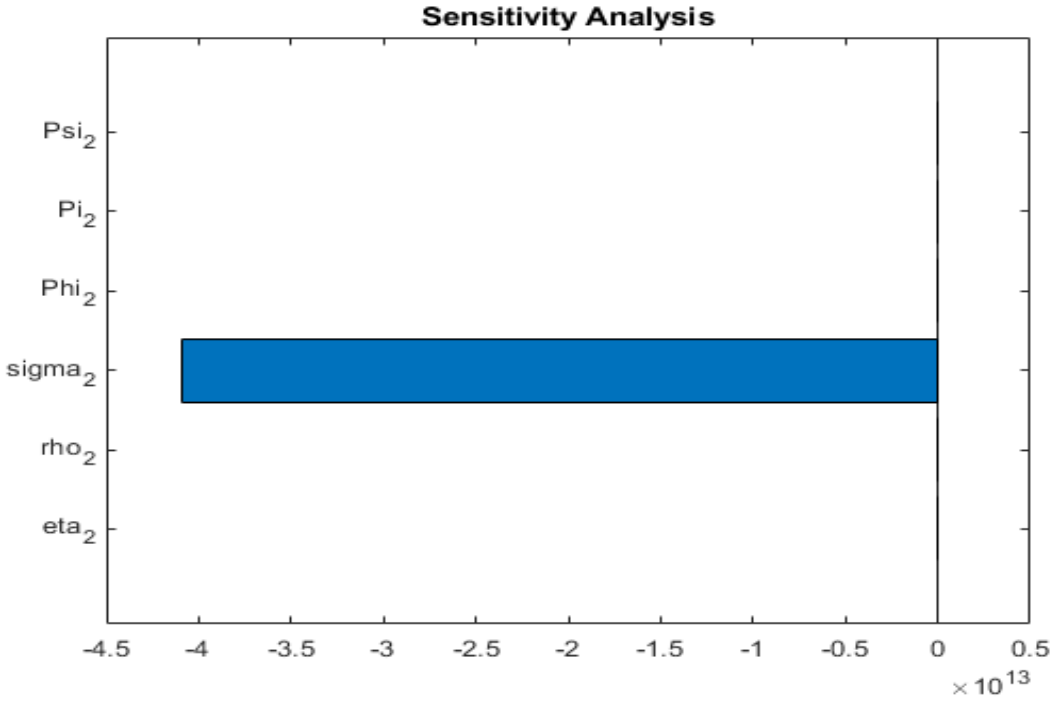
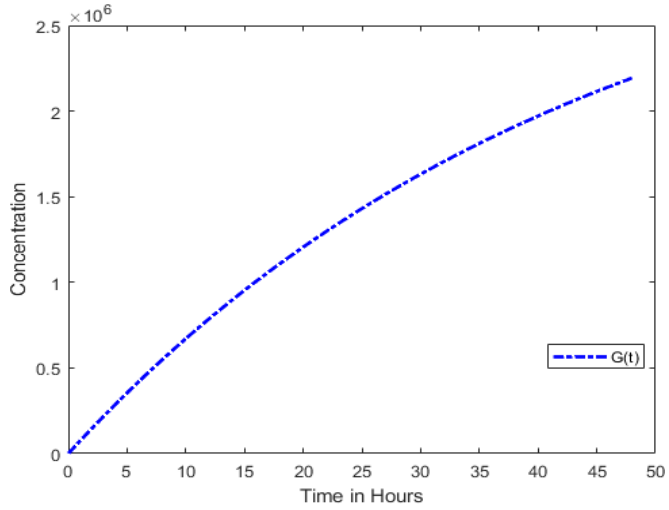


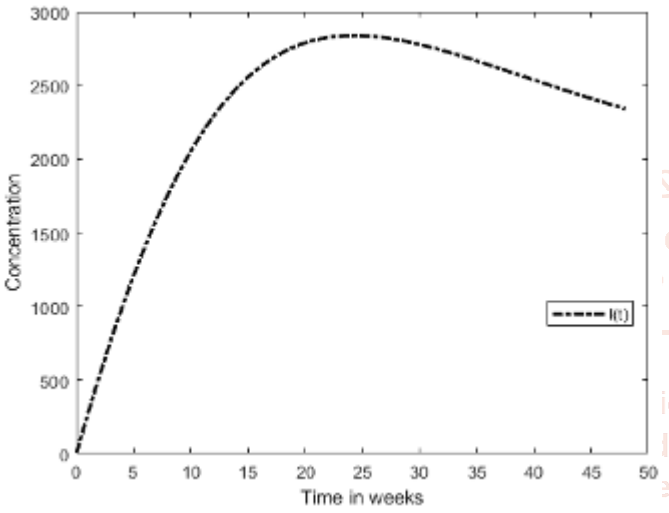
Figure 2: Sensitivity analysis showing σ_2 is the most sensitive. Thus, the constant rate of insulin-independent glucose disappearance is the most influential in the R_0.

5.3. Numerical Simulations of the model system

The numerical simulation shows the curves of the concentration of glucose and insulin. Figure 5.3 shows the glucose and insulin concentration curves. The curves indicate that insulin concentration increases faster than glucose concentration.



Glucose Concentration



Insulin Concentration

Figure 3: A plot of glucose and insulin concentration for a span of 48 hours.

Figure 3a shows a continuous glucose concentration growth throughout the 48 hours understudy. The observation implies that insulin production does not control glucose concentration since insulin concentration in Figure 3b concentration increases until 24 hours, then the curve begins to reduce. While the curve for insulin concentration begins to reduce, the curve for glucose concentration continues to increase. This clearly shows a need for an optimal control strategy to manage glucose concentration levels.

6. Optimal Control

A sensitivity analysis of the system presented in Figure 2 indicates that a constant rate of insulin-independent glucose disappearance σ_2 is the most sensitive in controlling glucose-insulin concentration. Therefore, we formulate optimal control that can be attained by increasing or reducing the σ_2. However, in this case, the objective function is to increase σ_2 to reduce or flatten the glucose concentration at some point.

If we let θ_2 be the constant rate of increase of σ_2, then a set of admissible θ_2 control is

$$\{\theta_2(t): [0,T] \to [0,1]\}. \quad (20)$$

6.1. The Extended Mathematical Control

To effectively reduce the glucose concentration, $\sigma_2 + \theta_2$ increases the overall constant rate of insulin-independent glucose disappearance, thus the extended model can be written as follows:

$$\begin{aligned} \frac{dG}{dt} &= \Pi_2 + \Psi_2 - ((\sigma_2 + \theta_2) + \eta_2 I)G \\ \frac{dI}{dt} &= \Phi_2 - \rho_2 I - \eta_2 IG \end{aligned} \quad (21)$$

with initial $G(t) > 0, I(t) > 0$. A successful control minimizes glucose concentration. Thus, the control $u = (\theta_2)$ is considered optimal if it minimizes the objective function defined as

$$j = \int_0^T (A_{12}[\Pi_2 + \Psi_2 - ((\sigma_2 + \theta_2) + \eta_2 I)G] + A_{22}\theta_2)dt \quad (22)$$

where A_{12}, A_{22} are the unit cost of increasing the insulin in the body per unit of time.

6.2. Minimization of the objective function

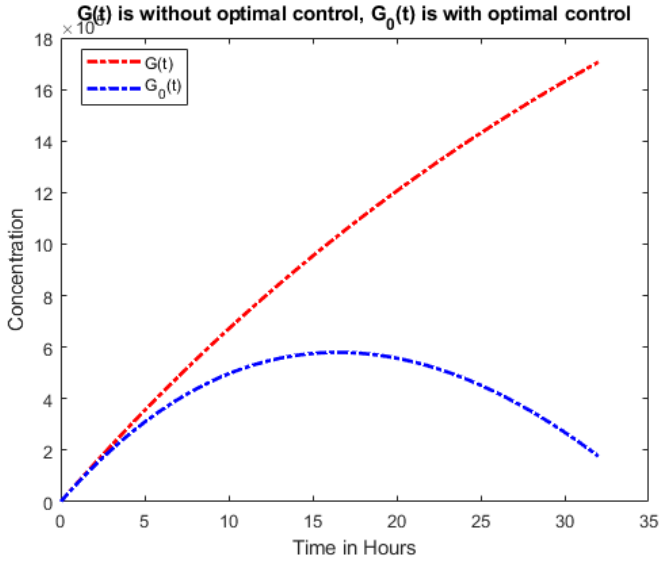
We employ Pontryagin's maximum principle and optimality conditions to obtain the solution to the optimal control problem (23) subject to (24).

$$\min_{0<\theta_2 \geq max_{\theta_2}} J = \int_0^T (A_1[\Pi_2 + \Psi_2 - ((\sigma_2 + \theta_2) + \eta_2 I)G] + A_2\theta_2)dt \quad (23)$$

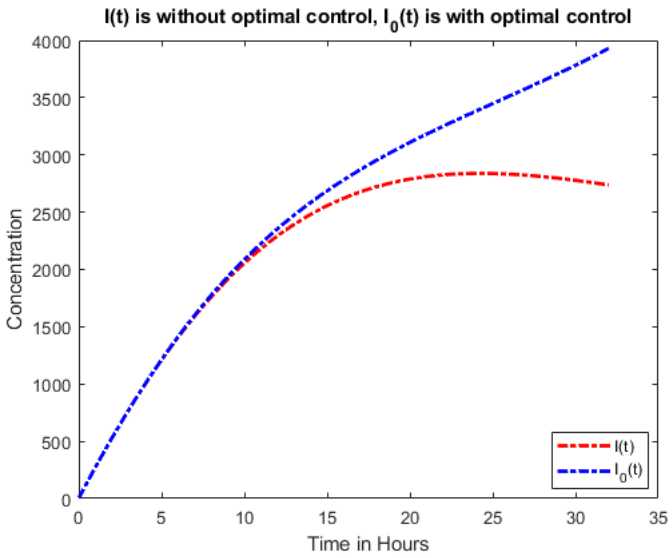
Subject to

$$\begin{aligned} \frac{dG}{dt} &= \Pi_2 + \Psi_2 - ((\sigma_2 + \theta_2) + \eta_2 I)G \quad : \quad G(0), I(0) > 0 \\ \frac{dI}{dt} &= \Phi_2 - \rho_2 I - \eta_2 IG \quad : \quad G(0), I(0) > 0 \end{aligned} \quad (24)$$

A numeral graphical solution to the problem is presented in Figure 4.



[a] Glucose Concentration



[b] Insulin Concentration

Figure 4: Glucose and insulin concentration before $G(t), I(t)$ and $G_0(t), I_0(t)$ after optimal control.

Figure 4 shows the effectiveness of the control parameter used. A comparison of Figure 6.2a indicates that glucose concentration increases continuously without optimal control. In optimal control, the glucose concentration increases to around the 15^{th} hour and then decreases continuously. Figure 4b indicates insulin concentration before $I(t)$ and after $I_0(t)$ optimal control. The concentration before the optimal condition is continuous, while after the concentration increases, the concentration growth reduces from around the 15^{th} hour. The observation in Figure 4 shows that the optimal control, increasing the constant rate of insulin-independent glucose disappearance, effectively reduces the glucose concentration from the 15^{th} hour.

7. Conclusion

The study presented a mathematical model formulating the concentration of glucose and insulin where extra glucose intake leading to extra stimulation of insulin production is considered. The study was motivated by the daily need to regulate glucose concentration in the body to manage Type-I diabetes. The well-posedness of the system indicated that the proposed model is applicable in real-life applications. Numerical simulation indicates that both glucose and insulin concentration continuously increases. This indicates a lack of optimality, a case that could persistently be type-I diabetes. A sensitivity analysis showed a constant rate of insulin-independent glucose disappearance is the most sensitive in the model. The study results observed that the extra glucose intake stimulates extra insulin production, causing the glucose concentration in the body to increase. This observation pointed to a need for optimal control based on the most sensitive parameter. We established optimal control based on a constant rate of insulin-independent glucose disappearance. The optimal control proved effective since the glucose curve decreases after 15^{th} hour. Future studies need to consider including other parameters, such as glucose accelerated loss due to exercise in the system.

Acknowledgement

The research work is supported by Kabote Adventist secondary school and the University of Eldoret (UoE).

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